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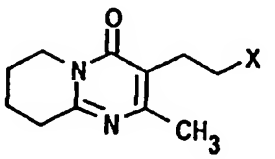
(54) Title: A PROCESS FOR THE PREPARATION OF ANTI-PSCHOTIC 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one



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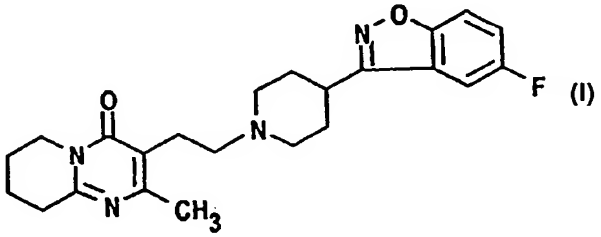

(I)

(57) Abstract: A process for the preparation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of formula (IIB) where X may be halo, acyloxy, or sulfonyloxy such as tosyloxy or mesyloxy, an intermediate in the synthesis of the anti-psychotic risperidone. The process comprises hydrogenation of 3-substituted ethyl-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one in aqueous inorganic acid medium at atmospheric to 60 psi at 0-100 °C in the presence of a metal catalyst and the product is isolated. A process for the preparation of risperidone of formula (I) comprising condensation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one with 6 fluoro-3-(4-piperidinyl)-1, 2-benzosoxazolein water in the presence of an inorganic base at 25 - 100 °C and the product is isolated.

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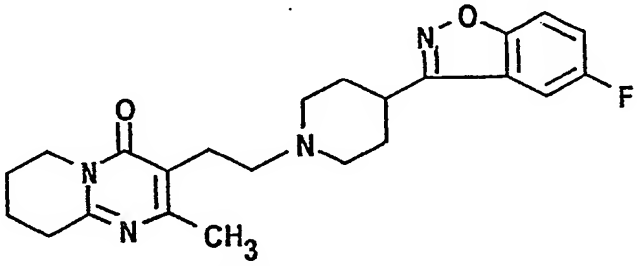
TITLE OF INVENTION

A process for the preparation of anti-psychotic 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one.

Technical field

The above compound is commonly known as risperidone and is of the formula I:

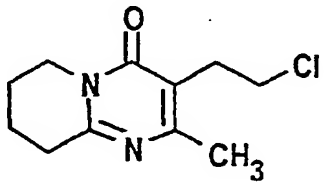


Formula I

Risperidone elicits its action by antagonising serotonine. Risperidone is a highly potent drug used in the treatment of schizophrenic states and also shows broader applications in other areas of psychosis.

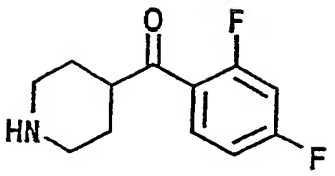
Background Art

Risperidone of the formula I is known to be prepared by the condensation of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido [1,2,-a]pyrimidin-4-one of the formula IIA:



Formula IIA

with 4-(2,4-difluorobenzoyl) piperidine of the formula III:



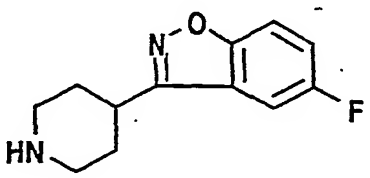
Formula III

in organic solvent such as methylene dichloride, acetonitrile, N,N-dimethyl formamide (DMF) or N-methyl pyrrolidone in the presence of an inorganic base such as sodium hydroxide, carbonate or bicarbonate at 50-100°C, followed by oximation and cyclisation (Spanish Patent No 2,050,069).

Inorganic bases used in the above reaction being sparingly soluble in organic solvent used as medium for the reaction, they may not neutralise the acid by-product fast with the result that the neutralisation may be sluggish. Due to the slow removal of the acid by-product from the reaction mixture, there are chances of decomposition of the condensation product, thereby reducing the yield and purity thereof. The yield of condensation product obtained by this condensation process is low of the order of 63.1%. This process is therefore inefficient and uneconomical. The medium for the condensation being organic, isolation of the condensation product is to be carried out by quenching the reaction mixture with water followed by extraction with organic solvent such as methylene dichloride. Solvent extraction is cumbersome, lengthy and time-consuming and also engenders poor recovery of organic solvent used for the reaction. Also organic solvents such as DMF are reported to decompose in the presence of inorganic bases at elevated temperatures (Encyclopedia of Chemical Technology, 3rd edition, 11, 263) further complicating isolation. Besides, use of organic solvents as medium for the reaction makes the process further expensive and uneconomical. Moreover, solvents such as DMF are hazardous and pollute

environment when used in large scale and also entail effluent disposal/treatment problems.

Risperidone of the formula I may also be prepared by the condensation of chlorotetrahydro pyridopyrimidine of the formula IIA with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole of the formula IV:

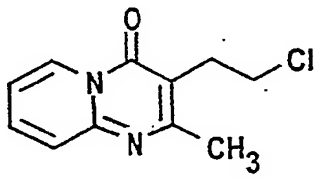


Formula IV

in an organic solvent such as DMF, 4-methyl-2-pentanone, benzene, ethanol, 1,4-dioxane, tetrahydrofuran, nitrobenzene or 1-methyl-2-pyrrolidinone in the presence of an organic base such as N,N-diethylethanamine, 4-ethyl morpholine or N-(1-methylethyl)-2-propanamine or an inorganic base such as sodium or potassium carbonate, sodium hydrogen carbonate or sodium methoxide, hydroxide or hydride, usually at 85 - 90°C (US Patent No 4804663). The organic bases which may be used in the above condensation are expensive and their use makes the above reaction uneconomical. Inorganic bases when used in organic solvent medium may result in decomposed condensation product as earlier discussed. The yield of the product obtained by this method is low of the order of 46% and renders the process inefficient and uneconomical. The reaction medium being organic, the isolation of the condensation product is to be carried out by quenching the reaction mixture with water followed by filtration of the resulting solid and recrystallisation thereof from an organic solvent such as DMF. This isolation procedure besides being cumbersome, suffers from poor solvent recovery. Also due to use of inorganic bases in organic solvent such as DMF, isolation

becomes further complicated for reasons as explained earlier. Organic solvents used as reaction medium further makes the process expensive and uneconomical. Also this process is not free from the disadvantages due to use of solvents such as DMF as aforesaid.

The intermediate chloro tetrahydro pyridopyrimidine of the formula IIA in the synthesis of anti-psychotic risperidone of the formula I may be obtained by hydrogenation of 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula VA:

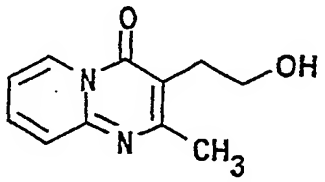


Formula VA

in acetic acid medium at 50 psi and at 25-30°C in the presence of Pd/C catalyst. (A Thesis entitled "Synthesis of Drugs & Drug Intermediates" submitted to "The University Of Mumbai" by Ms Evelyn D Lobo, p35, June 1996, for the degree of M Pharm Sci.). This hydrogenation may produce predominantly dechlorinated compounds as by-products, since dechlorination may be accelerated in acetic acid medium. This may result in low yield and purity of the product. The yield of the product obtained by this method is low of the order of 77%, thus making this process inefficient and uneconomical. The isolation of the product involves filtration of the catalyst followed by evaporation of acetic acid from the reaction mixture, dissolving the resulting residue in a solvent, deacidification and evaporation of solvent followed by recrystallisation of the resulting solid from 2-propanol. Such mutiple steps for isolation are cumbersome, lengthy and time consuming. Acetic acid is a hazardous and flammable solvent and pollutes the environment when used in

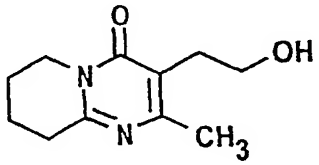
large scale. Also its use makes the process expensive and further uneconomical.

The chloro tetrahydro pyridopyrimidine reactant of the formula IIA may also be prepared by hydrogenation of the 3-(2-hydroxyethyl)-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula VI:



Formula VI

using Pd/C catalyst in aqueous ethanol at 25 - 30°C followed by reacting the resulting hydroxyethyl tetrahydro pyridopyrimidine compound of the formula VII :



Formula VII

with thionyl chloride in methylene chloride at 25-30°C for 24 hours (Spanish Patent No 2,050,069). This route involves two steps for the preparation of the compound of the formula IIA and is lengthy and time-consuming. Moreover, thionyl chloride is hazardous and when used in large scale, pollutes the environment. The overall yield of the product obtained by this method is low of the order of 44% due to two moderately yielding steps, thus making the process inefficient and uneconomical.

An object of the invention is to provide a process for the preparation of risperidone of the formula I, which is simple and less time consuming.

Another object of the invention is to provide a process for the preparation of risperidone of the formula I, which is inexpensive and economical.

Another object of the invention is to provide a process for the preparation of risperidone of the formula I, which results in high yield and purity of risperidone and is efficient.

Another object of the invention is to provide a process for the preparation of risperidone of the formula I, which is safe and does not pollute the environment.

Another object of the invention is to provide a process for the preparation of risperidone of the formula I, which is commercially feasible.

Another object of the invention is to provide a process for the preparation of tetrahydro pyridopyrimidine of the formula IIB, which is simple and less time consuming.

Another object of the invention is to provide a process for the preparation of tetrahydro pyridopyrimidine of the formula IIB, which is inexpensive and economical.

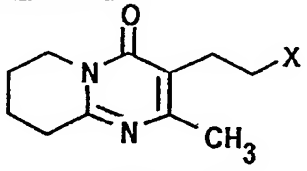
Another object of the invention is to provide a process for the preparation of tetrahydro pyridopyrimidine of the formula IIB, which results in high yield and purity of tetrahydro pyridopyrimidine and is efficient.

Another object of the invention is to provide a process for the preparation of chlorotetrahydro pyridopyrimidine of the formula IIB, which is safe and does not pollute the environment.

Another object of the invention is to provide a process for the preparation of chlorotetrahydro pyridopyrimidine of the formula IIB, which is commercially feasible.

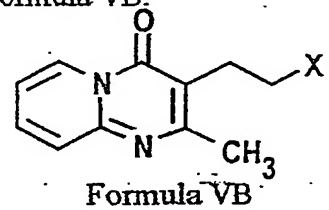
Disclosure of the invention

According to the invention there is provided a process for the preparation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula IIB:



Formula IIB

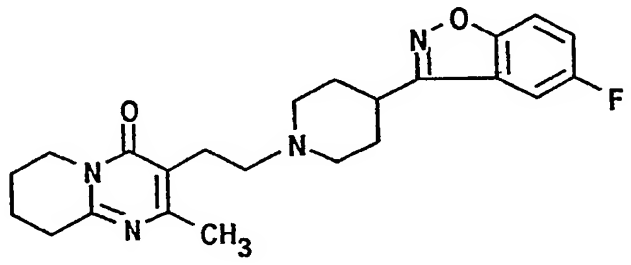
where X may be halo, acyloxy, or sulfonyloxy such as tosyloxy or mesyloxy, comprising hydrogenation of 3-substituted ethyl-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula VB:



Formula VB

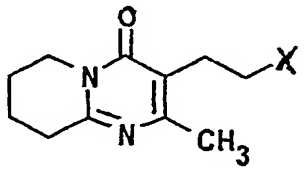
in aqueous inorganic acid medium at atmospheric to 60 psi at 0-100°C in the presence of a metal catalyst followed by isolation of the resulting product.

According to the invention there is also provided a process for the preparation of anti-psychotic 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one, commonly known as risperidone of the formula I:



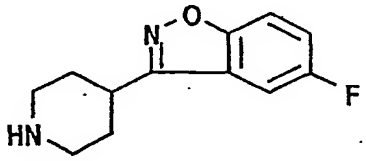
Formula I

comprising condensation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-one of the formula IIB:



Formula IIB

where X may be halo, acyloxy or sulfonyloxy such as tosyloxy or mesyloxy, with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole of the formula IV:



Formula IV

in water in the presence of an inorganic base at 25 - 100°C followed by isolation of the resulting product.

The compound of the formula IIB is an intermediate in the synthesis of the anti-psychotic risperidone.

The term halo includes chloro, bromo or iodo. Preferably X may be chloro.

The pyridopyrimidine compound of the formula VB may be prepared in known manner. (A thesis entitled "Synthesis of Drugs and Drugs Intermediates" submitted to "The University of Mumbai" by Ms Evelyn D Lobo, p 30, June 1996, for the degree of M Pharm Sci.).

The inorganic acid in the aqueous medium for the hydrogenation may be sulfuric acid, hydrochloric acid or hydrobromic acid, preferably hydrochloric acid. The inorganic acid solubilises the pyridopyrimidine

compound of the formula VB in aqueous medium by converting it to its water soluble salt, prior to hydrogenation.

The metal catalyst may be platinum, palladium, nickel, rhodium or ruthenium supported on solid support such as calcium carbonate, alumina, barium sulfate, silica or activated carbon. Preferably palladium supported on activated carbon may be used.

Preferably the reduction temperature may be 25 - 40°C.

Preferably the hydrogenaton is carried out at pressure of 25 psi.

The isolation of the tetrahydro pyridopyrimidine of the formula IIB may be carried out by filtration of the metal catalyst followed by pH adjustment to 4 - 10 of the resulting mixture with a base such as an alkali metal hydroxide or carbonate. The resulting solid is then filtered at 0 - 50°C, preferably at 10 - 20°C. Alternatively the filtrate after removal of catalyst, may be directly subjected to insitu condensation with the compound of the formula IV to produce risperidone.

The benzisoxazole compound of the formula IV may be prepared in known manner (US Patents Nos 4,355,037 and 4,804,663).

The inorganic base used in the condensation may be an alkali metal carbonate such as sodium, potassium or lithium carbonate or sodium bicarbonate or an alkaline earth metal carbonate such as calcium, barium or strontium carbonate or an alkali metal hydroxide such as sodium, potassium or lithium hydroxide or an alkaline earth metal hydroxide such as calcium, barium or strontium hydroxide. Preferably sodium carbonate may be used.

The condensation temperature may be preferably 60 - 90°C.

The isolation of risperidone from the reaction mixture is carried out by filtration at 25 - 40°C followed by purification, preferably by crystallisation using organic solvents such as DMF or N,N-dimethyl acetamide

or C_{1-3} aliphatic alkanol or ether such as diethyl ether or diisopropyl ether or tetrahydrofuran or ketone such as 2-propanone, 2-butanone or 4-methyl-2-pentanone, preferably DMF.

The process of the invention for the preparation of the tetrahydro pyridopyrimidine of the formula IIB is carried out in aqueous medium because of which it proceeds at a controlled rate. Therefore dechlorination of the compound of the formula IIB when X is chloro, is prevented. The process of the invention results in high yield (83%) and purity (99%) of the product of the formula IIB and is efficient and economical. The tetrahydro pyridopyrimidine compound of the formula IIB is obtained from a single step reaction and eliminates multiple steps for isolation as described in the prior art. The procedure to isolate the product of the formula IIB obtained by the process of the invention comprises filtration of the catalyst, pH adjustment and filtration of the resulting solid, and is therefore simple, less cumbersome. less tedious and less-time consuming when compared to the prior art methods. The compound of the formula IIB when subjected to insitu condensation makes the process for the preparation of risperidone further less time-consuming and economical. The process also eliminates hazardous solvents and pollution of the environment caused thereby and is safe to carry out. The use of water instead of organic solvents as medium for the reaction makes the process further inexpensive and economical and also eliminates solvent recovery/disposal/treatment problems as in the prior art. Due to the above reasons, this process is also commercially feasible.

According to the invention the process for the preparation of risperidone is carried out in an aqueous medium in the presence of an inorganic base. The solubility of the inorganic base in the aqueous medium

being high, the neutralisation of the acid by-product formed during the condensation is fast by the inorganic base in solution form. This prevents degradation of risperidone by the acid by-product and also results in high yields (66 - 72%) and purity (~99%) thereof, thereby making the process efficient and economical. The process of the invention does not use organic bases and is inexpensive. The reaction medium being aqueous, quenching with water or extraction with organic solvents is unnecessary for isolation of risperidone. The isolation procedure involves a single step ie filtration and is therefore simple, less cumbersome and less time-consuming when compared to the prior art methods. The process eliminates use of hazardous solvents and pollution of the environment caused thereby and is safe. The use of water as medium instead of organic solvents is inexpensive and economical and eliminates solvent recovery/disposal/treatment problems as in the prior art. Due to the above reasons, the process of the invention is commercially feasible.

The following experimental examples are illustrative of the invention but not limitative of the scope thereof.

Example 1

Preparation of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula II A :-

To a 500 ml hydrogenation flask was charged 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one (20.0 g, 99% pure by HPLC analysis), water (50.0 ml), 30% HCl (10.0 ml) and 10% Pd/C (2.0 g). The contents of the flask were reduced with hydrogen gas at pressure 25 psi under agitation for 6 hours at 30°C. The catalyst in the reaction mixture was filtered through Whatmann 1 filter paper. The filtrate free from catalyst was basified

by addition of 45% caustic soda lye (6.0 ml). The product was filtered and dried.

The product obtained was characterised by Nuclear Magnetic Resonance (NMR) Spectrosopy as follows:

^{1}H NMR (60 MHz), $CDCl_3$: δ 3.7 (m, 4H); δ 2.9 (t, J = 6Hz, 2H); δ 2.3 (s, 3H); δ 1.8 (m, 6H).

Yield = 16.6 g (83 %)

Purity = 99% [when analysed by High Performance Liquid Chromatography (HPLC)]

Example 2

Preparation of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a] pyrimidin-4-one (Risperidone of the formula I) : -

To a 10 L flask was charged the tetrahydro pyridopyrimidine (666.0 g) of Example 1, water (3330.0 ml) and 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazol (639.0 g) and sodium carbonate (1152.0 g). The contents of the flask were heated to 85 - 90°C and stirred for 4 hours. The reaction mixture was cooled to room temperature and filtered. The product was purified by crystallisation from DMF.

The product was characterised by NMR spectroscopic studies as follows:

^{1}H NMR (60 MHz, $CDCl_3$) : δ 7.5 - 7.9 (m, 1H); δ 6.8 - 7.45 (m, 2H); δ 3.8 -4 (m, 2H); δ 2.45 - 3.5 (m, 11H); δ 2.35 (s, 3H); δ 1.65 - 2.25 (m, 8H).

Yield = 865.0 g (72%)

Purity = 99% (when analysed by HPLC)

Example 3

Preparation of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a] pyrimidin-4-one (Risperidone of the formula I) by one-pot reaction : -

The filtrate free from catalyst of Example 1 was neutralised by addition of 45% caustic soda lye (5.5 ml) in a 250 ml flask. To it were charged 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (19.2 g) and sodium carbonate (34.6 g). The reaction mixture was heated to 85 - 90°C for 4 hours under stirring, cooled to room temperature and filtered. The cake was purified by crystallisation from DMF.

The product was characterised by NMR spectroscopic studies as follows:

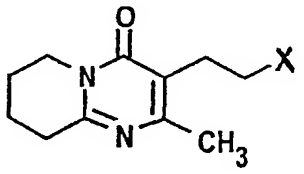
^{1}H NMR (60 MHz, $CDCl_3$) : δ 7.5 - 7.9 (m, 1H); δ 6.8 - 7.45 (m, 2H); δ 3.8 -4 (m, 2H); δ 2.45 - 3.5 (m, 11H); δ 2.35 (s, 3H); δ 1.65 - 2.25 (m, 8H).

Yield = 30.0 g (72%)

Purity = 99% (when analysed by HPLC)

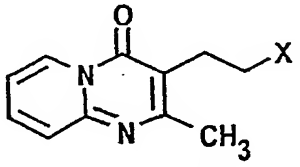
CLAIMS

1) A process for the preparation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula IIB:



Formula IIB

where X may be halo, acyloxy, or sulfonyloxy such as tosyloxy or mesyloxy, comprising hydrogenation of 3-substituted ethyl-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula VB:



Formula VB

in aqueous inorganic acid medium at atmospheric to 60 psi at 0-100°C in the presence of a metal catalyst followed by isolation of the resulting product.

2) A process as claimed in claim 1, wherein X is chloro.

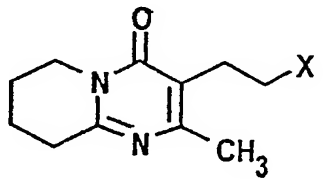
3) A process as claimed in claim 1 or 2, wherein the hydrogenation is carried out at pressure of 25 psi.

4) A process as claimed in any one of claims 1 to 3, wherein the inorganic acid is hydrochloric acid.

5) A process as claimed in any one of claims 1 to 4, wherein the hydrogenation is carried out at 25 - 40°C.

6) A process as claimed in any one of claims 1 to 5, wherein the metal catalyst is palladium supported on activated carbon.

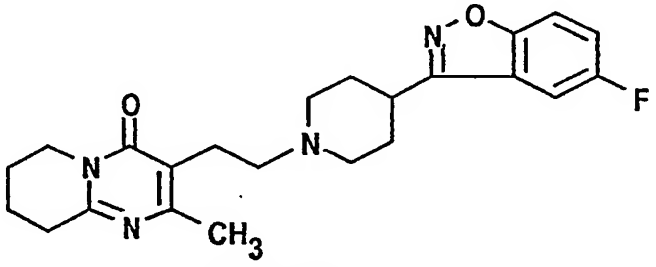
7) A process for the preparation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula IIB:



Formula IIB

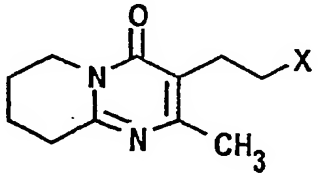
where X may be halo, acyloxy, or sulfonyloxy such as tosyloxy or mesyloxy, substantially as herein described particularly with reference to Example 1.

8) A process for the preparation of anti-psychotic 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one, commonly known as risperidone of the formula I:



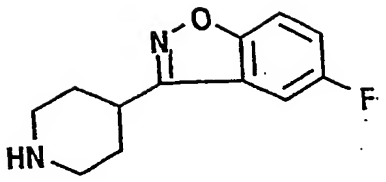
Formula I

comprising condensation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one of the formula IIB:



Formula IIB

where X may be halo, acyloxy or sulfonyloxy such as tosyloxy or mesyloxy, with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole of the formula IV:



Formula IV

in water in the presence of an inorganic base at 25 - 100°C followed by isolation of the resulting product.

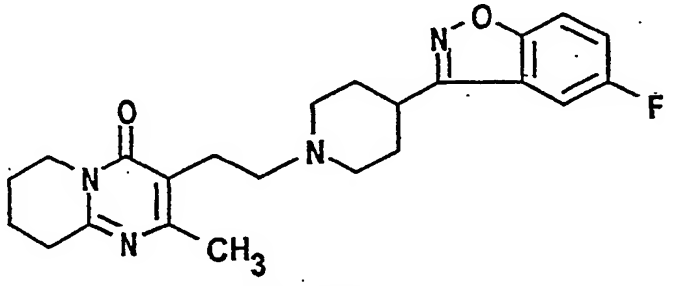
9) A process as claimed in claim 8, wherein X is chloro.

10) A process as claimed in claim 8 or 9, wherein the inorganic base is sodium carbonate.

11) A process as claimed in any one of claims 8 to 10, wherein the condensation is carried out at 60 - 90°C.

12) A process as claimed in any one of claims 8 to 11, wherein the purification during isolation is carried out by crystallisation fron DMF.

13) A process for the preparation of anti-psychotic 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2,-a]pyrimidin-4-one, commonly known as risperidone of the formula I:



Formula I

substantially as herein described particularly with reference to Examples 2 and 3.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 00/00053

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 471/04, 498/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, REGISTRY, WPI, EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ES 2074966 A1 (VITA-INVEST, S.A., SPAIN) 16 September 1995 (16.09.95) the whole document.	1-13
A	ES 2050069 A1 (VITA-INVEST, S.A., SPAIN) 1 May 1994 (01.05.94) the whole document. (cited in the application)	1-13
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A	EP 0196132 A2 (JANSSEN PHARMACEUTICA N.V., BELG.) 1 October 1986 (01.10.86) example 5. (cited in the application)	1-13

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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„O" document referring to an oral disclosure, use, exhibition or other means
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„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2000 (12.09.2000)	29 March 2001 (29.03.2001)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer MÜLLER-HIEL Telephone No. 1/53424/434

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 00/00053

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International application No.
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